Easy Access to Configurationally Controlled *C*-Glycofuranoside-Based Building Blocks by Means of Formyl *C*-Glycofuranosides

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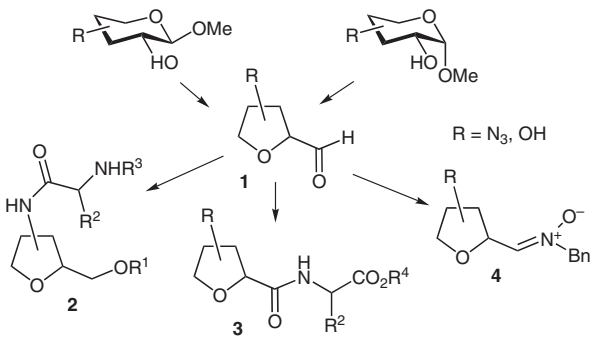
Abstract: A general approach to enantiopure *C*-glycofuranoside-based hybrid α/β-amino acids and nitrones, among other valuable building blocks, has been established via formyl *C*-glycofuranosides, easily available from hexose-derived equatorial-2-OH-glycopyranosides by DAST-promoted ring contraction.

Key words: *C*-glycofuranoside-based building blocks, formyl *C*-glycofuranosides, DAST-promoted ring contraction, *C*-glycofuranosyl nitrones, *C*-glycofuranosyl amino acids

The replacement of the exocyclic carbon–oxygen or carbon–nitrogen bond of native glycoconjugates with a carbon–carbon bond creates compounds which are resistant to chemical and enzymatic degradation with minimal loss or enhancement in biological activity with respect to the parent *O*- or *N*-glycosides.[1] Therefore the ready access to *C*-glycosides is of great interest in carbohydrate chemistry.[2]

A major problem to prepare functionalized *C*-glycosides relies on the few available anomeric carbon–carbon bond-forming reactions endowed with both chemical efficiency and stereocontrol. This problem could be avoided by the use of C-functionalized carbohydrate derivatives bearing an α- or β-linked highly reactive carbon functionality at the anomeric center. Following this idea, we have developed by means of formyl *C*-glycofuranosides **1**, a wide-scope method for the synthesis of configurationally controlled *C*-glycofuranoside-based building blocks containing the substructures **2**–**4** (Scheme 1), from which an easy access to biologically relevant more complex *C*-glycofuranoside-based molecules (*C*-oligosaccharides and *C*-glycoconjugates) is provided. The key step in this strategy is clearly a DAST-mediated rearrangement reaction that involves ring contraction of hexose-derived equatorial 2-OH-glycopyranosides, and leads to formyl *C*-glycofuranosides under remarkably mild conditions. This methodology allowed us to prepare a series of formyl *C*-glycofuranosides,[3] and from the point of view of atom economy[4] it can be considered in the carbohydrate field as a greener formylation methodology than those strategies that are based on the use of formyl anion equivalents.[5] We have employed formyl *C*-glycofuranosides **1** as key intermediates via reductive amination of the formyl group for the synthesis of enantiopure N-substituted 1-*C*-aminomethyl glycofuranosides **5** (Figure 1).[6]

Herein we describe the synthesis of some enantiopure biologically relevant *C*-glycofuranoside-based building blocks (*C*-GfBB), in particular 1-*C*-alkoxymethyl glycofuranosyl amino acids **2**, *C*-glycofuranosylcarbonyl amino acids **3**, and *C*-glycofuranosyl nitrones **4** in good to high yields.



Scheme 1

Compounds of types **2** and **3** are structural and configurationally related to the natural antifungal antibiotic cispentacin (**6**),[7] which has been used as a peptidomimetic for proline. Amino acids **2** and **3** are of potential interest in the field of peptide foldamers as heterogeneous α/β-peptide subunits. α/β-Hybrid peptides containing α- and β-amino acid constituents in 1:1 backbone alternation display a variety of helical structures[8] and some of these peptides elicit substantial biological activity.[9] Diversity is supplied by readily available α-amino acids, while conformational stability and specificity are provided by the preorganized β-amino acid residues (e.g., **6** and **7**, Figure 1).[10]

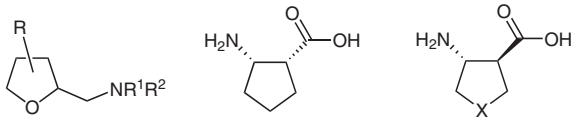


Figure 1

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The synthetic utility of nitrones **4** as 1,3-dipolar systems[11] is demonstrated by the highly stereoselective preparation of *C*-disaccharides, sugar moieties of which are tethered through a rigid five-membered heterocycle.

Scheme 2 summarizes our synthetic strategy for the preparation of *C*-glycofuranoside-based building blocks (*C*-GfBB) with substructures **2**–**5** via formyl *C*-glycofuranosides, readily available as their synthetic equivalents, from a hexose-derived equatorial 2-OH-glycopyranoside, for example, methyl α-D-allopyranoside **8**.[12]

Treatment of compound **8** with diethylaminosulfur trifluoride (DAST) in refluxing acetonitrile for 12 minutes as described previously[6] gave the 2,5-anhydro-1-fluoro-1-*O*-methyl-D-altritol **9** (73%), as an epimeric mixture which contains a masked formyl function, and therefore can be considered as a synthetic equivalent of the formyl *C*-glycofuranoside **13** (Table 1, entry 1).

To obtain the methoxymethyl glycofuranosyl glycine derivative **16**, having the substructure **2**, and its precursor the vicinal amino alcohol **15** we followed route A starting from compound **9** (Table 1).

Thus, reduction of **9** dissolved in dry THF, with sodium cyanoborohydride (12.7 mol equiv) in the presence of 3 Å molecular sieves (r.t., 15 min, and then HCl–Et_2O, 5 min), afforded compound **10**[13] in 64% yield, which was subjected to Staudinger reaction to give the amine **15** (95%, entry 3). On its turn, Staudinger reaction of **10**, by using Boc-Gly-OH, gave the dipeptidomimetic **16** in high yield (entry 4). It is noteworthy that the ^{1}H NMR coupling constants of compound **16** contrast sharply with those expected for a furanose ring, suggesting a conformational deviation. Thus, the $J_{2,3}$ value of 8 Hz observed matched with a dihedral angle H2–C2–C3–H3 next to 0°, and the $J_{4,5}$ = 3 Hz is remarkably lower than the corresponding usual value (7.5–8.5 Hz) observed for a furanose ring.[3,6] Preliminary molecular-mechanic calculations[14] show a sole low-energy conformer (below 10 kJ/mol, Figure 2) with a dihedral angle (17–23°) in agree with NMR data indicated above.

Targeting the formyl *C*-glycofuranoside synthetic equivalent **12**,[6] which is a key product for the synthesis (route B)

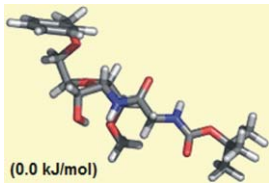
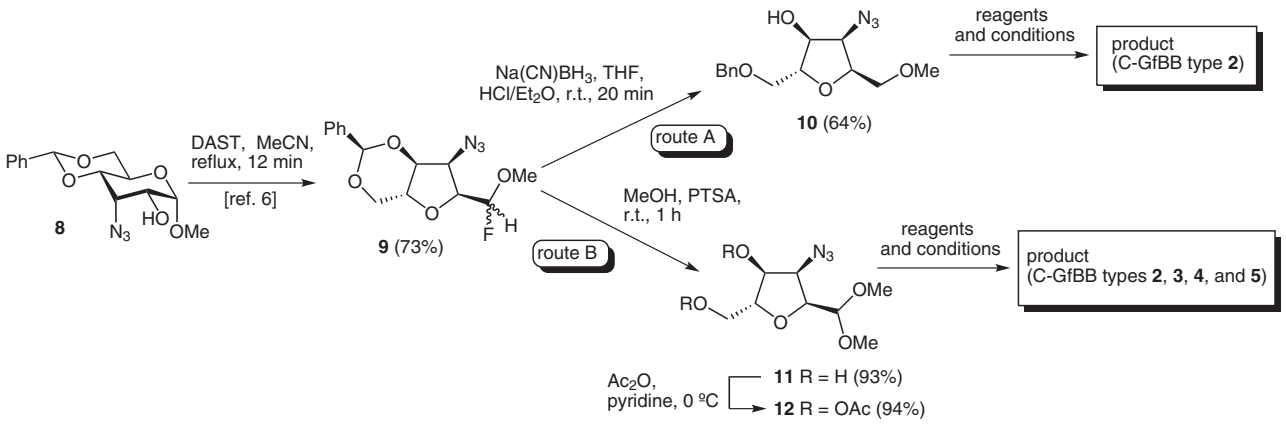


Figure 2 Lowest energy conformer and relative energy (0.0 kJ/mol) of compound **16**[14]

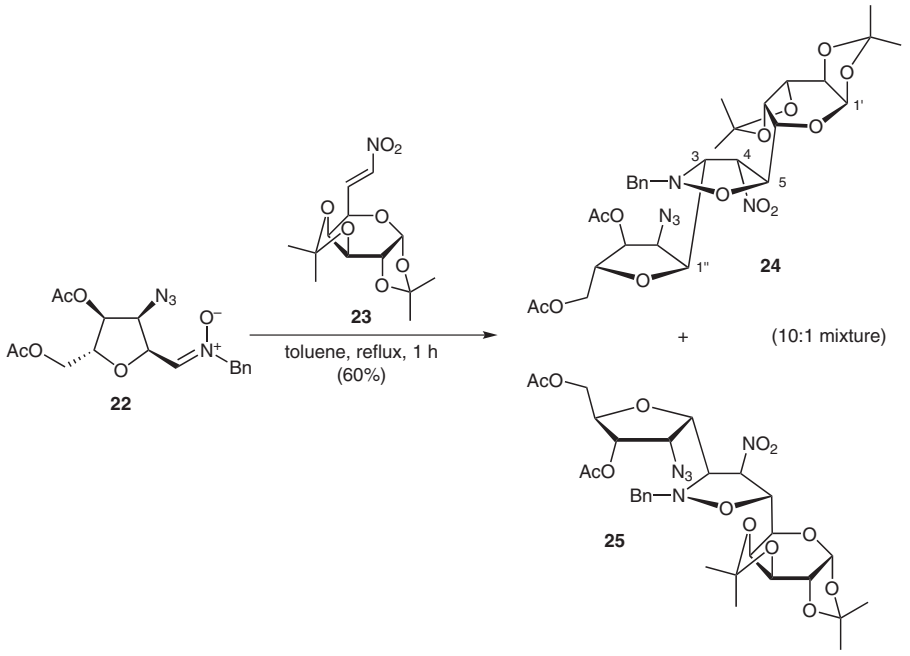
of *C*-GfBB having substructures **3**–**5**, compound **9** was transformed (PTSA–MeOH) into the 4,6-O-deprotected dimethyl acetal **11** (93%). When this crude product was subjected in situ to standard acetylation conditions, the 4,6-di-*O*-acetyl derivative **12** was obtained in high yield (94%).[6] Hydrolysis of **12** with TFA–H_2O (9:1) gave aldehyde **14** (entry 2), from which a variety of protected *C*-glycofuranosyl diamines **17** (substructure **5**) were obtained by reductive amination with diverse primary or secondary amines (entry 5).[6]

The *C*-glycofuranosyl β-amino acid precursor **19** (entry 7) was obtained from the key compound **12** by hydrolysis of the acetal function and subsequent oxidation with Jones reagent or starting from the primary alcohol **18** (Jones reagent, –30 °C, r.t., 1 h, 72%). On its turn, **18** was prepared (entry 6) by treatment of the crude aldehyde **14** obtained in situ by hydrolysis [TFA–H_2O (9:1), r. t., 1 h] of the dimethyl acetal **12**, with imidazole (1.4 mol equiv) and $NaBH(OAc)_3$ (1.4 mol equiv) in dry DCE.[6] Transformation of **19** into **20** was easily achieved for protected glycine (EDCI, HOBt, DIPEA, HCl·EtO-Gly-NH_2, CH_2Cl_2, r.t., 18 h) in good yield (entry 8).

The *C*-glycofuranosyl nitrone **21** was obtained in poor yield (22%, entry 9) by treatment of the crude aldehyde **13** prepared in situ (PTSA, acetone, r.t., 1 h) from **9**, with Bn-NHOH·HCl and $NaHCO_3$ ($MgSO_4$, dry CH_2Cl_2, 4 Å MS, r.t., 5 h). However, starting from the di-O-acetylated dimethyl acetal **12**, the nitrone **22** was obtained (entry 10) in good yield (67%), thus opening potential access to long-chain functionalized *C*-disaccharides through isoxazolidine derivatives.[15] For instance, the 1,3-dipolar cycloaddition reaction of **22** with the D-galactose derived nitroolefin **23** led to the 3,5-di-*C*-glycosyl-4-nitroisoxazo-



Scheme 2 Synthetic routes to *C*-glycofuranoside-based building blocks (*C*-GfBB, types **2**–**5**) via formyl *C*-glycofuranosides (see Table 1)



Scheme 3

lidines **24** and **25** (60%, Scheme 3) as a 10:1 mixture (^{1}H NMR).[16] The configuration assignment was made on the basis of the stereospecificity of the cycloaddition reactions, and the *exo*/*endo* and facial stereoselectivities observed for related reactions.[17]

In summary, a practical approach to the synthesis of enantiopure, biologically relevant *C*-glycofuranosides, in particular protected 1-*C*-alkoxymethyl glycofuranosyl amino acids, *C*-glycofuranosyl amino acids, and *C*-glycofuranosyl nitrones, via formyl *C*-glycofuranosides is reported. Moreover, the synthetic utility of some of them for the preparation of more complex *C*-glycofuranoside-based molecules is provided. Our strategy: 1) offers operational simplicity, 2) allows complete stereocontrol at the anomeric center, and 3) has the potential to enable the preparation of a wide range of multifunctional *C*-glycofuranoside-based building blocks from diverse easily available hexose-derived equatorial 2-OH-glycopyranosides, by a DAST-promoted ring contraction as the key step.

Table 1 Formyl *C*-Glycofuranosides and *C*-Glycofuranoside-Based Building Blocks (*C*-GfBB)

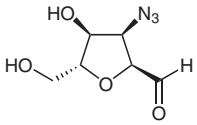
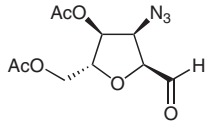
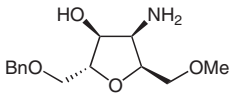
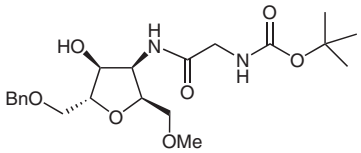
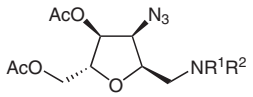
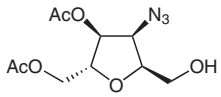
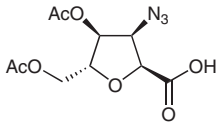
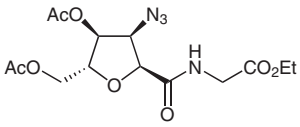
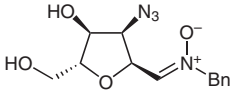
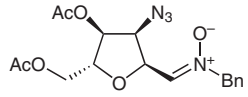
Entry	Route	Substrate	Reagents and conditions	Products (yield, %)[a]
1	–	**9**	PTSA, acetone, r.t., 1 h	 **13** (83)
2	B	**12**	TFA–H_2O (9:1), r.t., 1 h	 **14** (90)
3	A	**10**	1. Ph_3P, THF, r.t., 8 h 2. H_2O, 20 h	 **15** (95)

Table 1 Formyl *C*-Glycofuranosides and *C*-Glycofuranoside-Based Building Blocks (*C*-GfBB) (continued)

Entry	Route	Substrate	Reagents and conditions	Products (yield, %)[a]
4	A	**10**	1. Ph_3P, THF, r.t., 8 h 2. EDCI, HOBt, DIPEA, Boc-Gly-OH, CH_2Cl_2, r.t., 20 h	 **16** (82)
5	B	**12**	1. TFA–H_2O (9:1), r.t., 1 h 2. RNH_2 or R^1R^2NH, $NaBH(OAc)_3$, DCE, 25 °C	 **17**[6] (35–88)
6	B	**12**	1. TFA–H_2O (9:1), r.t., 1 h 2. $NaBH(OAc)_3$, imidazole, DCE, 25 °C, 20 h	 **18**[6] (56)
7	B	**12**	1. TFA–H_2O (9:1), r.t., 1 h 2. Jones' reagent, –30 °C to r.t.	 **19**[3] (65)
8	B	**12**	1. TFA–H_2O (9:1), r.t., 1 h 2. Jones reagent, –30 °C to r.t. 3. EDCI, HOBt, DIPEA, HCl·EtO-Gly-NH_2, CH_2Cl_2, r.t., 18 h	 **20** (67)
9	–	**9**	1. PTSA, acetone, r.t., 1 h, 83% 2. BnNHOH·HCl, $NaHCO_3$, $MgSO_4$, MS 4 Å, CH_2Cl_2, r.t., 5 h, 26%	 **21** (22)
10	B	**12**	1. TFA–H_2O (9:1), r.t. 1 h 2. BnNHOH·HCl, $NaHCO_3$, $MgSO_4$, MS 4 Å, CH_2Cl_2, r.t., 40 min	 **22** (67)

[a] All products were fully characterized by their IR, ^{1}H NMR (500 MHz), ^{13}C NMR (125.7 MHz), and HRMS spectral data.[18]

Acknowledgment

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(13) **Preparation and More Relevant Data of Compound 10**
A soln of **9** (105 mg, 0.340 mmol) in dry THF (4.8 mL) containing 3 Å MS was treated with $NaCNBH_3$ (273 mg, 4.35 mmol). The mixture was stirred for 15 min, and then Et_2O–HCl (3.5%, 6 mL) was added. After 5 min, the reaction was diluted with H_2O (20 mL) and CH_2Cl_2 (20 mL). After separation, the organic layer was successively washed with sat. aq $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated. Column chromatography (hexane–EtOAc, 3:1) gave pure **10** (64 mg, 64%).
Analytical Data
$[\alpha]_D^{24}$ +16.2 (*c* 0.63, CH_2Cl_2). IR: ν_{max} = 2108 (N_3) cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): δ = 7.36–7.26 (m, 5 H, Ph), 4.75 (s br, 1 H, OH_{C4}), 4.55 (s, 2 H, CH_2Ph), 4.55–4.53 (m, 1 H, H-4), 4.17 (ddd, 1 H, $J_{1,2} = J_{1',2}$ = 5.7 Hz, $J_{2,3}$ = 3.7 Hz, H-2), 4.14 (dd, 1 H, $J_{3,4}$ = 4.2 Hz, H-3), 3.93 (ddd, 1 H, $J_{4,5}$ = 7.5 Hz, $J_{5,6'}$ = 4.5 Hz, $J_{5,6}$ = 3.0 Hz, H-5), 3.65 (dd, 1 H, $J_{6,6'}$ = 11.0 Hz, H-6), 3.58 (dd, 1 H, H-6′), 3.56 (dd, 1 H, $J_{1,1'}$ = 10.0 Hz, H-1), 3.43 (dd, 1 H, H-1′), 3.31 (s, 3H, OCH_3) ppm. HRMS (CI): *m/z* calcd for $C_{14}H_{19}N_3O_4$ + H: 294.1454; found: 294.1462.

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(16) The ratio of **24/25** was calculated by the ^1H NMR ($CDCl_3$) of the mixture, in particular from the signals of H-4 of both stereoisomers: δ = 5.65 ppm (dd, 1 H, $J_{4,5}$ = 7.8 Hz, $J_{3,4}$ = 4.5 Hz, H-4) observed for the major stereoisomer **24**, and that observed at δ = 4.80 ppm (dd, 1 H, $J_{4,5}$ = 7.2 Hz, $J_{3,4}$ = 4.8 Hz, H-4) for **25**.

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(18) **More Relevant Data**
Compound **16**: $[\alpha]_D^{21}$ +37 (*c* 0.77, acetone). ^1H NMR (500 MHz, acetone-d_6): δ = 7.36–7.33 (m, 5 H, Ph), 7.09 (d, 1 H, $J_{NH,3}$ = 7.0 Hz, CCONH), 6.43 (s br, 1 H, OCONH), 4.58–4.53 (m, 1 H, H-3), 4.57 and 4.58 (each 2 d, 1 H, $J_{H,H'}$ = 12.9 Hz, CH_2Ph), 4.45 (d, 1 H, $J_{OH,4}$ = 8.0 Hz, OH_{C4}), 4.31 (ddd, 1 H, $J_{2,3}$ = 8.0 Hz, $J_{1',2}$ = 4.5 Hz, $J_{1,2}$ = 3.0 Hz, H-2), 4.17–4.14 (m, 1 H, H-4), 4.01 (ddd, 1 H, $J_{5,6} = J_{5,6'}$ = 4.0 Hz, $J_{4,5}$ = 3.0 Hz, H-5), 3.77 (dd, 1 H, J_{gem} = 16.5 Hz, $J_{NH,CH2a}$ = 6.0 Hz, NHCH^a_2), 3.72 (dd, 1 H, $J_{NH,CH2b}$ = 6.0 Hz, NHCH^b_2), 3.55 (dd, 1 H, $J_{6,6'}$ = 10.5 Hz, H-6), 3.52 (dd, 1 H, H-6′), 3.50 (dd, 1 H, $J_{1,1'}$ = 10.5 Hz, H-1), 3.40 (dd, 1 H, H-1′), 3.35 (s, 3 H, OCH_3), 1.43 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (125.7 MHz, acetone-d_6): δ = 170.5, 157.0, 139.6-128.2, 85.2, 79.6, 78.9, 73.8, 73.1, 72.9, 72.0, 59.3, 53.9, 44.9, 28.6 ppm. HRMS (CI): *m/z* calcd for $C_{21}H_{32}N_2O_7$ + H: 425.2288; found: 425.2291. Anal. Calcd for $C_{21}H_{32}N_2O_7$: C, 59.42; H, 7.60; N, 6.60. Found: C, 59.12; H, 7.45; N, 6.72.
Compound **20**: $[\alpha]_D^{24}$ +52 (*c* 0.66, CH_2Cl_2). IR: ν_{max} = 2114 (N_3) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.07 (dd, 1 H, $J_{NH,CH2a}$ = 5.0 Hz, NH), 5.22 (dd, 1 H, $J_{4,5}$ = 8.5 Hz, $J_{3,4}$ = 4.5 Hz, H-4), 4.68 (dd, 1 H, $J_{2,3}$ = 4.5 Hz, H-3), 4.62 (d, 1 H, H-2), 4.40–4.36 (m, 1 H, H-5), 4.36 (dd, 1 H, $J_{6,6'}$ = 12.5 Hz, $J_{5,6}$ = 2.5 Hz, H-6), 4.23 (q, 2 H, *J* = 7.0, C_2H_5), 4.13 (dd, 1 H, $J_{5,6'}$ = 4.0 Hz, H-6′), 4.11 (dd, 1 H, J_{gem} = 18.0 Hz, NHCH^a_2), 4.07 (dd, 1 H, NHCH^b_2), 2.16, 2.09 (2 s, each 3 H, $COCH_3$), 1.29 (t, 3 H, C_2H_5) ppm. HRMS (CI): *m/z* calcd for $C_{14}H_{20}N_4O_8$ + H: 373.1359; found: 373.1349.
Compound **22**: $[\alpha]_D^{24}$ –1.2 (*c* 0.75, CH_2Cl_2). IR: ν_{max} = 2112 (N_3) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.41 (s, 5 H, Ph), 6.79 (d, 1 H, $J_{1,2}$ = 4.5 Hz, H-1), 5.20 (dd, 1 H, $J_{4,5}$ = 8.0 Hz, $J_{3,4}$ = 5.0 Hz, H-4), 5.15 (dd, 1 H, $J_{2,3}$ = 4.5 Hz, H-2), 4.94 (dd, 1 H, H-3), 4.91 (s, 2 H, CH_2Ph), 4.34 (dd, 1 H, $J_{6,6'}$ = 12.0, $J_{5,6}$ = 3.0 Hz, H-6), 4.24 (ddd, $J_{5,6'}$ = 4.5 Hz, H-5), 4.04 (dd, 1 H, H-6′), 2.14, 2.08 (2 s, each 3 H, 2 $COCH_3$) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 170.7, 170.2, 136.2, 132.0-129.2, 77.2, 77.0, 73.5, 69.3, 63.3, 62.7, 20.9, 20.4 ppm. HRMS (CI): *m/z* calcd for $C_{17}H_{20}N_4O_6$ + H: 377.1461; found: 377.1454.